REVIEW

Hypothalamic–Pituitary–Adrenal Dysfunction in Posttraumatic Stress Disorder

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Neuroendocrine studies examining the hypothalamic–pituitary–adrenal (HPA) axis under baseline conditions and in response to neuroendocrine challenges have supported the hypothesis of altered HPA functioning in posttraumatic stress disorder (PTSD). However, to date, there is much debate concerning the nature of HPA changes in PTSD. Furthermore, in studies showing parallel findings in PTSD and major depressive disorder there is controversy regarding whether the HPA alterations suggest a specific pathophysiology of PTSD, or, rather, reflect comorbid major depressive disorder. This review summarizes findings of HPA axis dysfunction in both PTSD and major depressive disorder, and shows distinct patterns of HPA changes, which are probably due to different mechanisms of action for cortisol and its regulatory factors.

Introduction

The major rationale for studying the hypothalamic–pituitary–adrenal (HPA) axis in posttraumatic stress disorder (PTSD) is that the HPA axis is one of the major hormonal systems mediating the stress response (Selye 1936; Mason 1968). Because PTSD is a stress reaction, fundamental changes in the HPA axis are likely relevant to its pathophysiology.

An additional reason for studying the HPA axis in PTSD is the overlap in symptoms between PTSD and major depressive disorder, such as the insomnia, impaired concentration, social withdrawal, and loss of interest. Depressed mood is often an adjunctive symptom of PTSD; moreover, several studies have documented a very high incidence of comorbid major depressive disorder with PTSD (Robins 1974; Helzer et al 1979; Sierles et al 1983; Pitts 1985; Davidson et al 1985; Southwick et al 1991). Strong evidence exists for disturbance of the HPA axis in major depressive disorder (Kathol 1985; Gold et al 1988; Nemeroff 1991).

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Given PTSD's association with both "stress" and depression, it is not surprising that HPA abnormalities have been reported in PTSD (Kudler et al 1987; Smith et al 1989; Halbreich et al 1989; Yehuda et al 1990a; Pitman and Orr 1990; Kosten et al 1990; Yehuda et al 1991). However, as reviewed below, the abnormalities observed do not appear to parallel the hypercortisolemia seen in major depressive disorder or acute stress reactions. Rather, many studies have provided evidence to support an underactivity of the HPA axis in PTSD. Prior to reviewing the actual clinical studies of HPA axis alterations in PTSD and major depressive disorder, we summarize preclinical information regarding HPA functioning in chronic stress in order to provide a theoretical framework for HPA axis abnormalities observed in PTSD.

HPA Dysregulation in Chronic Stress

The primary function of HPA activation in stress is to rapidly produce glucocorticoids from the adrenals. Stress-activated neurotransmitter systems in the brain release CRF from the hypothalamus, which in turn stimulates the release of ACTH from the pituitary and cortisol from the adrenals. Cortisol and other glucocorticoids then initiate the suppression of other immune, metabolic, and neural defensive reactions that occur in response to stress (Munck et al 1984; Munck and Guyre 1986), and also act via a negative feedback loop to the hippocampus, hypothalamus, and the pituitary to regulate the subsequent hormone release. Immune, metabolic, and neural defensive biological responses are important for the short-term response to stress, but would produce long-term damage to the organism if they were not eventually terminated. For example, prolonged, elevated concentrations of glucocorticoids can also be toxic, and are associated with several other detrimental consequences such as neuronal death (Sapolsky et al 1985), medical diseases (Munck et al 1984), and impaired affect and cognitive activity (Ling et al 1981; Wolkowitz et al 1990).

The phenomenon of stress is generally associated with an overactivation of the HPA axis, and a resultant increase in glucocorticoids; however, there is evidence that the HPA axis may become underactive under certain conditions of repeated or chronic stress, likely reflecting a physiological adaptation of the HPA axis. In these studies, the paradigm of chronic stress consists of the daily, repeated administration of the same stressor. Thus, in rats, the daily administration of stressors including injection of formaldehyde (Stark et al 1968; Mikulaj et al 1973), ether exposure (Riegle 1973), forced swimming (Frenkl et al 1969), noise (Armario et al 1985), immobilization (Riegle 1973; Kawakami et al 1972; Natelson et al 1988; Pitman et al 1988), and cold (Daniels-Severs et al 1973) leads to a gradual attenuation of the adrenocortical response to stress. The time required for this "adaptation" varies from 2 to 6 weeks depending on the nature of the stressor. The attenuated corticosterone release is not thought to be due to adrenal atrophy because rats that have adapted to chronic or repeated stress can show substantial increases in corticosterone when placed in a novel or acute stressful situation (Sakellaris et al 1975). Additionally, the response appears to be stress-specific in that some chronic stressors appear to consistently produce elevations in glucocorticoids without showing diminished adrenocortical responses over time (Stark et al 1968; Daniels-Severs et al 1973; Armario et al 1985; Pitman et al 1988). Importantly, factors such as severity (Pitman et al 1990), controllability (Seligman 1975), and/or predictability (Katz 1981, 1984; Katz et al 1981; Katz and Sibel 1982; Ottenweller et al 1989) of the chronic stressor may impede habituation to chronic stress. Thus, animals subjected to a chronic regimen of unusually intense

or varying stressors do not show attenuated pituitary-adrenocortical responses over time (Katz 1981, 1984; Katz et al 1981; Katz and Sibel 1982; Ottenweller et al 1989).

Studies of pituitary responsiveness have also supported the notion of decreased HPA activation to chronic stress (Dallman et al 1973; Amir and Amit 1979; Young and Akil 1985a, 1985b; Ottenweller et al 1989). Pituitary glands of rats subjected to repeated 30-min foot shock for 14 days do not show a blunted ACTH response to vasopressin or CRF in vivo, as do pituitaries from rats receiving acute stress (Young and Akil 1985a). Pituitary adaptation to stress may occur much more rapidly than the corticosterone adaptation to chronic stress, with adaptation occurring as early as several hours following continuous stress (Rivier and Vale 1987). As in the case with adrenocortical responses to chronic stress, superimposition of a novel acute stressor can increase the attenuated ACTH levels following chronic stress (LeMevel et al 1979; Vernikos et al 1972).

In primates repeated and continuous exposure to a conditioned avoidance stress over a 6-week period results in a suppressed cortisol secretion below baseline levels (Mason 1965). As with rodents, the glucococorticoid response to stress can be increased by strengthening the intensity of the stress, or superimposing a novel acute stress (Mason et al 1968). In humans, chronic combat exposure and the prolonged threat of imminent enemy attack has been associated with lower than normal cortisol secretion in a battalion of soldiers studied while stationed in Vietnam (Bourne et al 1967, 1968; Rose et al 1968). Low basal urinary cortisol excretion has also been observed in parents of chronically, fatally ill children (Friedman et al 1963), and in humans exposed to highly stressful, chronic, occupational tasks (Vernikos-Danellis et al 1975). In both preclinical and clinical studies, the low glucocorticoid levels appear to reflect a chronic adaptation in stress-induced HPA activation in the form of a heightened negative feedback sensitivity at the level of the hippocampus, hypothalamus, or pituitary, perhaps as a compensatory mechanism to prevent the harmful sequelae of chronically elevated glucocorticoid levels.

An attenuated corticosterone response to stress has also been observed in rats with a prior history of chronic stress exposure. For example, Katz demonstrated that adult rats who had been chronically stressed with a regimen of several types of stressors over a 21-day period showed a reduced corticosterone and behavioral response to subsequent acute noise stress (Katz 1981). Armario et al (1988) demonstrated that repeated chronic stress in adult rats impaired the ACTH adaptation to a subsequent novel chronic stressor, whereas behavioral manifestations of stress, such as stress-induced body weight inhibition, were attenuated by prior chronic stress exposure.

Chronic stress exposure in the neonatal period can have profound effects on subsequent HPA responses to stress. Adult animals that have received chronic neonatal stress show a lower baseline corticosterone level (Hess et al 1969) and an attenuated corticosterone secretion to novel stress (Levine et al 1967; Haltmeyer et al 1967; Hess et al 1969). A lower corticosterone response to stress has also been observed in rats stressed in the postweanling period (Ader 1970). These studies suggest that early contact with environmental stress may alter the response of the HPA axis to subsequent stress. The mechanism for this response to subsequent stress may involve an altered sensitivity of brain (i.e., hippocampal) glucocorticoid receptors, possibly produced during the period of initial stress. It is now well established that the physiological actions (McEwen et al 1976; Olpe and McEwen 1976; McEwen 1977), and the behavioral effects of glucocorticoids [i.e., performance on passive avoidance responses to stress (Bohus and deKloet 1977)], are directly mediated by glucocorticoid receptors. Several studies have recently demonstrated that early exposure to handling stress results in a permanently increased hippocampal

glucocorticoid receptor concentration in rat brain (Meaney et al 1985a, 1985b, 1989). A larger than normal number of glucocorticoid receptors would potentially allow for a stronger glucocorticoid negative feedback, resulting in a more sensitive HPA axis and a faster recovery from acute stress (Meaney et al 1989). Thus, from a cellular perspective, the low cortisol levels following chronic stress may reflect a chronic adaptation in stress-induced HPA activation in the form of a heightened negative feedback sensitivity at the level of the hippocampus, hypothalamus or pituitary, perhaps as a compensatory mechanism to prevent the harmful sequelae of chronically elevated glucocorticoids (Meaney et al 1988).

In addition to molecular explanations for the low cortisol in response to chronic stress, there have also been behavioral and psychosomatic perspectives on this finding. For example, there has been the suggestion from behavioral neuroendocrine studies that pituitary adrenocortical activation may increase behaviors associated with terminating stress in rats. In some preclinical studies, high corticosterone levels have been associated with superior passive avoidance learning (Lissak et al 1957; Levine et al 1970), but not increased active avoidance (Mason 1968; Levine et al 1970). This observation has led to the suggestion that corticosteroids may act to increase the ability of organisms to cope with stress by normalizing the increased arousal in limbic midbrain structures (Bohus 1973; Bohus and deWied 1978) in response to stress. Thus, an increase in corticosteroids would lead to a more adaptive active avoidance coping behavior, and a decrease in glucocorticoids would tend to result in a more passive avoidance behavior (Vernikos-Danellis and Heyback 1980). In human studies, there has also been considerable emphasis on the relationship between hormonal responses to stress and coping mechanisms (Mason 1968; Wolff et al 1964; Poe et al 1970; Knight et al 1979; Frankenhaueser 1975). In the aggregate, this research has lead to the suggestion that hormonal levels may reflect not only state changes, such as emotional arousal or distress, but also more enduring trait or style characteristics including those linked to coping mechanisms (Wolff et al 1964; Poe et al 1970; Knight et al 1979; Frankenhaueser 1975; Funkenstein et al 1954; Mason 1975; Williams 1983; Kosten et al 1984; Nesse et al 1984).

Chronic Stress and PTSD

The direction of HPA responses to stress may depend on the interaction of several factors, including the nature of the stressor (i.e., with respect to chronicity, severity, controllability, and predictability) and the previous stress history of the organism. One of the complexities in neuroendocrine research in PTSD to date has been an inability to clarify the precise type of "stress" being examined. On the one hand, to produce the disorder of PTSD, an individual must experience stress of great magnitude (traumatic stress), which may have been acute *or* chronic in nature. However, the development of PTSD in and of itself indicates the presence of a chronic aftermath of the stress, and the resultant behavioral and clinical sequelae may be chronically stressful in their own right or leave the individual more sensitive to subsequent stress. Furthermore, individuals who develop PTSD in response to trauma may be more vulnerable to the development of a stress disorder because of genetically based vulnerability and/or pretraumatic stress histories. Thus, it is possible that HPA abnormalities in PTSD would be similar to those observed in preclinical studies of chronic stress or early stress.

For the purpose of this review, HPA axis abnormalities in PTSD are compared with findings in major depressive disorder. Our aim is to suggest that HPA axis abnormalities

Table 1. 24-hr Urinary Cortisol Excretion in PTSD

Study	PTSD Group	Comparison Group
Mason et al (1986)[a]	33 μg/day (n = 9)	76 μg/day (n = 26) Depression
Pitman et al (1990)[b]	107 μg/day (n = 20)	80 μg/day (n = 15) Combat controls
Yehuda et al (1990a)[b]	42 μg/day (n = 16)	62 μg/day (n = 16) Normal controls

[a]PTSD was diagnosed according to DSM-III.
[b]PTSD was diagnosed according to DSM-III-R using the SCID.

in PTSD do not simply reflect symptoms of major depressive disorder or of acute, nonspecific stress. Rather, HPA alterations in PTSD reflect a unique pathophysiology of this disorder consistent with previous stress research.

Measures of HPA Activity in PTSD and Major Depressive Disorder

Both naturalistic and challenge strategies have been used to assess HPA activity in PTSD and major depressive disorder. Naturalistic studies have involved measuring basal hormone levels from the particular gland of interest, for example, cortisol secretion from the adrenals. However, given that the HPA system is a self-regulating one, absolute basal hormonal levels may not be definitive. Endocrine challenge studies have been employed to identify particular defects in the HPA axis that might be obscured by the self-regulation of the HPA axis under basal conditions. One type of challenge measures endocrine responses to oral administration or infusion of a synthetic hormone [i.e., dexamethasone or corticotrophin-releasing-hormone (CRF)].

More recently, increasing attention has been paid to the evaluation of steroid receptor binding characteristics. Lymphocyte glucocorticoid receptors appear to parallel changes in less accessible tissue such as brain (Lowy 1989). An understanding of steroid receptor binding parameters is critical to a proper interpretation of studies examining both basal hormone secretion and hormonal responses to challenges, because hormones cannot exert their genomic effects unless they are bound to steroid receptors. Thus, measures of ambient hormone concentration alone do not reflect the effects of steroids on target tissue.

The four type of investigations reviewed below are: studies of urinary cortisol excretion, lymphocyte glucocorticoid receptor number, cortisol responses to dexamethasone, and ACTH responses to CRF infusion in both PTSD and major depressive disorder. Although in some cases investigators have suggested that HPA alterations in PTSD resemble those observed in major depressive disorder, we believe that these two disorders show quite distinct HPA abnormality profiles.

Studies of Urinary Cortisol Excretion

Studies of major depressive disorder have almost consistently shown an increase in plasma and urinary glucocorticoids in depressed patients compared with normal controls and other psychiatric groups (Gibbons and McHugh 1962; McClure 1966; Sachar et al 1973; Mason et al 1986; Kathol et al 1989). In the PTSD literature there are three reports of 24-hr urinary-free cortisol excretion, and the results are mixed (Table 1). In a pilot study, Mason et al (1986) reported significantly lower mean 24-hr urinary cortisol excretion in PTSD inpatients than in four other psychiatric diagnostic groups, including major de-

pressive disorder. The mean urinary-free cortisol excretion was 33 μg/day in PTSD compared with 50 μg/day in major depressive disorder (in endogenously depressed patients the mean was 76 μg/day ($n = 26$; Mason, unpublished data). In a second study, Yehuda et al (1990a) studied 16 unmedicated inpatients and outpatients with PTSD and 16 non-psychiatric, healthy controls. The mean urinary-free cortisol for the combined inpatient/outpatient sample was 42 μg/day compared with 62 μg/day for normal controls. In this study, the effect of comorbid major depressive disorder on urinary-free cortisol was also evaluated. The mean urinary-free cortisol excretion from PTSD patients with major depressive disorder was not significantly different from the mean urinary-free cortisol excretion of PTSD patients without major depressive disorder. Data from these two studies suggest a lower basal activity of the HPA axis in PTSD, even in PTSD patients with a concurrent major depressive disorder. These findings are contrary to the hypercortisolemia observed in major depressive disorder.

In contrast to these two reports, Pitman and Orr (1990) reported that 24-hr urinary excretion was higher in PTSD outpatients than veteran combat controls. The mean cortisol excretion reported was 107 μg/day for the PTSD group and 80.5 μg for the combat controls. These values are at the very high end for normal 24-hr cortisol excretion, and importantly, are substantially higher than those reported for both PTSD and normals in the two other published studies. One explanation for the relatively high cortisol values in Pitman and Orr's study may be the method of collecting the urine specimens. Mason et al (1986) and Yehuda et al (1990a) collected urine on dry ice, whereas Pitman and Orr collected the urine at room temperature and used an acid preservative (to prevent degradation of catecholamines, which were also measured). Acidification of the urine may promote hydrolysis of the unconjugated cortisol, yielding artificially high cortisol values (Mason et al 1986). Furthermore, acid treatment can interfere with the antibody–antigen reaction in the radioimmunoassay procedure and thus result in artificially high cortisol values (personal communication, Clinical Assays Laboratories). Finally, failure to perform extraction of steroids with methylene chloride prior to radioimmunoassay can yield estimates of cortisol that may be as much as threefold higher than those obtained when steroids are extracted prior to assay (personal communication, Clinical Assays Laboratories).

Although methodological differences can account for the overall greater cortisol values compared with other studies, it is still necessary to interpret the main finding in Pitman and Orr's (1990) study, namely that PTSD patients showed a significantly higher mean cortisol excretion compared with the control group. In this regard it is important to note that Pitman and Orr's (1990) study was fundamentally different from those conducted by Mason et al (1986) and Yehuda et al (1990a) in that this study used combat controls instead of normal volunteers. Because combat controls are ostensibly free from manifest symptoms of PTSD, they represent a good comparison group for determining whether neuroendocrine changes are associated with *current* symptomatology. However, it may be that combat controls are different in basal HPA activity from normal volunteers. Combat controls, by definition, are individuals who have undergone the chronic stress of combat, and perhaps have met diagnostic criteria in the past for PTSD. As such, these individuals could conceivably show HPA adaptation reflected in ambient cortisol excretion. In order to resolve this issue, studies using all three groups (combat controls, individuals with PTSD, normal volunteers) should be performed. In such studies, the combat control group should be carefully evaluated for lifetime diagnosis of PTSD and other psychiatric conditions.

Other issues relating more directly to cortisol metabolism, and which could contribute to changes in urinary-free cortisol levels in PTSD, should also be evaluated in subsequent studies. Steady-state cortisol levels are the result of ACTH-induced synthesis and release of cortisol from the adrenal gland as well as the metabolism and clearance of cortisol. It is often assumed that increases or decreases in plasma or urinary cortisol levels are due solely to changes in cortisol synthesis. Although there is evidence for a hypothalamic and/or pituitary abnormality contributing to the HPA dysregulation in PTSD (discussed below), it is also possible that increases in the metabolism of cortisol may contribute to the diminution of HPA activity in some patients.

The advantage of urinary cortisol studies over plasma sampling studies is the relative ease with which one can obtain estimates of the biologically active fraction of cortisol (i.e., the portion of cortisol that is not bound to corticosteroid binding globulin). In major depressive disorder, several studies have shown increases in plasma cortisol concentrations, however, corticosteroid binding globulin and plasma free cortisol levels have been reported to be normal in depressed patients when compared with controls (Schlechte and Hamilton 1987). To our knowledge there are no reported studies measuring corticosteroid binding globulin or plasma-free cortisol in PTSD patients. This is an important consideration, especially in regards to interpreting cortisol-induced changes in glucocorticoid receptors (see below) and other biological systems.

Lymphocyte Glucocorticoid Receptor Number

In recent years investigators have measured lymphocyte glucocorticoid receptors as a way to further explore the hypercortisolism in major depressive disorder. In both preclinical and clinical studies, circulating corticosteroid concentrations have been found to produce dynamic changes in glucococorticoid receptor number in a variety of target tissues, including brain (Sapolsky et al 1984; McEwen et al 1986) and lymphocytes (Schlechte and Sherman 1982; Schlechte et al 1982). The regulation of glucococorticoid receptors by hormones is thought to be adaptive. For example, in acute stress, a decrease in glucocorticoid receptor number in response to increased cortisol secretion potentially minimizes the harmful effects of glucocorticoids (Sapolsky et al 1984). In contrast, in endocrinopathies such as Cushing's disease, increased cortisol secretion is not accompanied by corresponding decreases in glucocorticoid receptors (Kontula et al 1980; Junker 1983). Thus, the hypercortisolemia ultimately leads to the detrimental consequences of this disorder (Lowy et al 1989).

Because circulating corticosteroid concentrations contribute to the regulation of steroid receptors it has been hypothesized that the increased cortisol levels observed in major depressive disorder might be associated with a decrease in the number of glucocorticoid receptors in neurons and/or lymphocytes (Gormley et al 1985; Whalley et al 1986; Lowy et al 1989). Alternatively, it has been suggested that the primary defect in major depressive disorder is a faulty regulation of glucocorticoid receptors within the HPA axis that alters the feedback signal of circulating steroids, possibly leading to an increased synthesis and release of CRF and ACTH (Lowy et al 1989). Supporting these hypotheses is the observation that depressed patients do not show the physical signs of hypercortisolism that are typically seen in patients with Cushing's syndrome, suggesting that glucocorticoid resistance may have developed (Lowy et al 1989). In addition, other hormonal systems such as prolactin are insensitive to dexamethasone-induced suppression in depressed patients (Meltzer et al 1982).

Some (Gormley et al 1985; Whalley et al 1986; Lowy et al 1989), but not all (Schlechte and Sherman 1985; Wassef et al 1990) studies have shown a decrease in the number of glucocorticoid receptors/lymphocyte in major depressive disorder. One study reported a significant association between reduced lymphocyte glucocorticoid receptors and subsequent nonsuppression in response to 1 mg dexamethasone (Gormley et al 1985). In considering the relationship between lymphocyte and neuronal glucocorticoid receptors it should be noted that many similarities between lymphoid and neuronal glucocorticoid receptors have been reported in animal studies. For example, high concentrations of glucocorticoid receptors are found in both types of tissue, which are similar in receptor affinity and steroid specificity (Lowy 1989). Lymphoid and neuronal glucocorticoid receptors also share some common regulatory mechanisms: for example, adrenalectomy in rats produced increases in both lymphocyte and hippocampal glucocorticoid receptor number (Lowy 1990).

In a pilot study, Yehuda et al (1991) reported a larger number of lymphocyte glucocorticoid receptors in patients with PTSD compared to normal controls. These data, although preliminary, are consistent with the observed decreases in urinary cortisol excretion, and suggest an attenuated activation of the HPA axis in this disorder. Lymphocyte cytosolic glucocorticoid receptor number and plasma cortisol concentration were measured at 8:00 AM and 4:00 PM. Glucocorticoid receptor number was 63% greater in the morning and 26% greater in the afternoon in the 15 PTSD patients compared with the normal volunteer group. Both groups showed a morning-to-afternoon decline in glucocorticoid receptor number that paralleled the normal diurnal decline in cortisol secretion. Glucocorticoid receptors and plasma cortisol levels were not correlated. Morning glucocorticoid receptor number was positively correlated with PTSD symptoms and anxiety symptoms, but not with depressive symptoms, suggesting that changes in glucocorticoid receptors are not likely due to adjunctive symptoms of depression. The strong relationship between glucocorticoid receptor number and severity of PTSD symptoms suggested that the biological alterations observed may be directly relevant to pathophysiological aspects of PTSD.

Cortisol Responses to Dexamethasone

Studies examining the cortisol response to 1 mg of dexamethasone in major depressive disorder have repeatedly shown a "nonsuppression" of cortisol in about 40%–60% of depressed patients (for a comprehensive review of this literature see Carroll et al 1981, 1982; APA Task Force 1987). The DST involves the administration of 1 mg dexamethasone at 11:00 PM, when normal cortisol secretion is at its nadir in the diurnal cycle. Dexamethasone is a synthetic glucocorticoid that mimics the effect of cortisol, and acts directly on the hypothalamus, and pituitary to inhibit the release of CRF and ACTH, respectively. Ultimately the inhibition of CRF and ACTH results in a decrease in the amount of cortisol released from the adrenal, so at 9 and 17 hr following the oral administration of 1 mg dexamethasone, cortisol secretion is substantially lowered in normal individuals. The high dose of 1 mg usually suppresses cortisol to a level of under 5 μg/dl plasma in normals at 8:00 AM and remains at that level at 4:00 PM. Either a reduced ability of glucocorticoids to suppress the release of CRF and ACTH, or adrenal cortisol hypersecretion will result in maintained high levels of cortisol in response to dexamethasone.

The specific mechanism underlying DST nonsuppression in major depressive disorder

is thought to be an increased activity of the entire limbic-HPA system, leading, via an enhanced secretion of CRF and other related neuropeptides, to an exaggerated ACTH and glucocorticoid secretion (Bardeleben et al 1985). Excessive glucocorticoid levels then reduce steroid receptor density at several sites of the feedback system, including the hypothalamus and hippocampus, thus reducing the responsiveness of the system to steroids (DeKloet and Reul 1987). In this regard, it is interesting that the one study that has directly examined lymphocyte glucocorticoid receptor number in response to dexamethasone administration in depressed patients showed a decrease in lymphocyte glucocorticoid receptors in patients who suppressed cortisol, but not in dexamethasone nonsuppressors (Gormley et al 1985).

Four studies to date have investigated the cortisol response to the standard 1 mg DST in PTSD. In these studies normal dexamethasone suppression is defined as cortisol concentration below 5 μg/dl at 4:00 PM. The studies all report that, in contrast to the nonsuppression to dexamethasone observed in major depressive disorder, PTSD patients without major depression showed a "normal" suppression to dexamethasone (Kudler et al 1987; Kosten et al 1990). In PTSD patients meeting criteria for major depressive disorder the results are less clear. One study reported a 50% rate of nonsuppression in PTSD patients who also met diagnostic criteria for major depressive disorder (Kudler et al 1987), and another study found a 32% rate of nonsuppression among depressed PTSD patients (Olivera and Fero 1990). These data tend to suggest that PTSD patients with major depressive disorder show similar HPA axis alterations compared with patients with major depression alone. On the other hand, the other two published reports failed to observe dexamethasone nonsuppression in any of the PTSD patients with major depressive disorder (Halbreich et al 1989; Kosten et al 1990). The discrepancy among these four studies in the rate of dexamethasone nonsuppression in depressed PTSD patients is puzzling because the methodology entailed in performing DST studies is quite straightforward. Thus, differences between published reports may be related to differences in the diagnosis and classification of major depressive disorder across studies. However, none of the above studies measured dexamethasone levels, which have been shown to be important in the interpretation of the DST (Lowy and Meltzer 1987).

Despite the fact that some individuals with PTSD do appear to show nonsuppressive responses to dexamethasone, if the DST literature is considered in the aggregate, a close examination of the studies reveals that PTSD patients may in fact show an *exaggerated* response to dexamethasone, that is, a response opposite to the nonsuppression observed in major depressive disorder. To illustrate this more clearly, data of 4:00 PM postdexamethasone cortisol values from the four studies are presented in Table 2. If the mean cortisol data across all published studies are summed and averaged, the overall average cortisol value in nondepressed PTSD subjects would be 1.74 μg/dl. If the means were weighted to reflect the actual number of subjects evaluated, the mean cortisol value of the 69 PTSD patients across all studies would be 1.05 μg/dl. This value is well below the established cutoff of 5.0 μg/dl. In averaging the 4:00 PM postdexamethasone cortisol values of the 93 PTSD patients with comorbid depression the overall mean is higher, that is, 248 μg/dl, but still well below the cutoff of 5.0 μg/dl used cortisol in major depressive disorder. Interestingly, in considering the literature as a whole, meta-analysis reveals that the mean cortisol secretion at 4:00 PM following dexamethasone is significantly higher in the PTSD group with major depressive disorder ($Z = 6.8$; $p = 0.0001$).

Because the DST studies were designed to test the hypothesis of "nonsuppression" in PTSD, most of the studies have not focused on the possibility of an exaggerated cortisol

Table 2. DST Findings in PTSD

Studies of PTSD without MDD	μg/dl CORT	*n*	Nonsuppressors (%)
Kudler et al (1987)	1.86 ± 1.87	18	6
Kosten et al (1990)	2.38 ± 2.58	7	13
Olivera and Fero (1990)	1.00 ± 0.10	44	0
Averaging across all subjects, the mean cortisol level is 1.05 μg/dl (n = 69).			
Studies of PTSD with MDD[a]	μg/dl CORT	*n*	Nonsuppressor (%)
Kudler et al (1987)	3.83 ± 3.15	10	50
Olivera and Fero (1990)	2.70 ± 2.78	65	32
Halbreich et al (1990)	0.96 ± 1.63	14	0
Kosten et al (1990)	0.90 ± 0.53	4	0
Averaging across all subjects, the mean cortisol level is 2.48 μg/dl (n = 93).			

[a]Diagnoses of major depressive disorder were made using RDC criteria in Kudler et al. Halbreich et al. and Kosten el al. and using DSM-III criteria in Olivera et al. PTSD was diagnosed according to DSM-III criteria in all four studies.

response, or "supersuppression" to dexamethasone. In the study by Halbreich et al (1989), the possibility of a supersuppression to dexamethasone was discussed. The investigators reported that the mean 4:00 PM cortisol for the PTSD group was 0.96 μg/dl, for the normal controls the mean was almost 2.0 μg/dl, and for the major depressive disorder group without PTSD the mean cortisol was 4.74 μg/dl. Although the difference between the PTSD and normal control groups was not statistically significant, the authors felt that the difference between the groups might be meaningful in suggesting a hyperresponsivity to dexamethasone in PTSD. Such a response would be consistent with both low ambient cortisol levels and increased glucocorticoid receptor number, and would represent again, a distinct response from that observed in major depression.

ACTH Responses to CRF

A major question in elucidating hypothalamic–pituitary–adrenal dysfunction in major depressive disorder has concerned possible changes in hypothalamic secretion of CRF in mediating hypercortisolemia. Specifically, hypothalamic secretion of CRF is thought to be increased in major depressive disorder, although it has been very difficult to demonstrate this directly (Gold et al 1986). Nemeroff and colleagues demonstrated hypothalamic hypersecretion of CRF by examining the concentration of this peptide in cerebrospinal fluid (Nemeroff et al 1984; Banki et al 1987). This finding has recently been replicated by Risch et al (1991). Kling et al (1991) failed to observe CSF CRF concentrations, but this group did report that concentrations of CRF in cerebrospinal fluid are correlated with other indices of HPA axis metabolism (Roy et al 1987).

A more accessible method of examining hypothalamic hypersecretion in depression has involved using the CRF challenge test (Gold and Chrousos 1985; Gold et al 1986; Holsboer et al 1985, 1986). The CRF challenge test measures the pituitary adrenocorticotropin hormone (ACTH) and adrenal cortisol response to exogenous infusion of CRF. An attenuated ACTH production in response to exogenous CRF is consistent with hypercortisolemia stemming from CRF hypersecretion (Gold and Chrousos 1985).

Table 3. HPA Alterations in PTSD and MDD

	PTSD	MDD
Urinary cortisol excretion	↓	↑
Cortisol response to DEX	↓	↑
ACTH response to CRF	↓	↓
Glucocorticoid receptors	↑	↓

To date, the CRF challenge test has been the best way to evaluate both hypothalamic CRF secretion and pituitary ACTH activity. Without the use of this challenge test, baseline ACTH levels would probably appear deceptively "normal" in response to chronic hypothalamic hypersecretion of CRF. This is because under conditions of CRF hypersecretion, the pituitary gland would mediate between hypothalamic ACTH stimulation and the inhibition of ACTH resulting from the negative feedback of adrenal corticosteroids (Lowy et al 1989). The result would be a "normal" concentration of ACTH but a sensitized pituitary gland. By giving exogenous CRF it is possible to test for an altered sensitivity of the pituitary gland. The acute response to administered CRF would be an increased ACTH production. However, in the context of hypercortisolemia, the ACTH response to CRF infusion would be attenuated.

Investigators have tended to show that the normal rise in ACTH in response to CRF is attenuated in major depressive disorder (Gold and Chrousos 1985; Gold et al 1986; Holsboer et al 1985, 1986). The blunted ACTH response typically occurs in hypercortisolemic patients, and is thought to reflect a decreased number of pituitary CRF receptors caused by hypothalamic CRF hypersecretion (Gold et al 1986; Holsboer et al 1986; Nemeroff et al 1988), and/or an increased negative feedback inhibition of the pituitary secondary to abnormally high circulating cortisol levels (Lowy et al 1984, 1989).

A single study of eight PTSD subjects suggests that the ACTH response to CRF is also blunted (Smith et al 1989). However, the mechanisms underlying the blunted ACTH response in PTSD are likely to be different from the mechanism described above for major depressive disorder, because the attenuated ACTH response in PTSD patients occurred in the presence of normal, not elevated evening plasma cortisol levels. Instead, the attenuated ACTH response to CRF in PTSD may be due to a decreased pituitary sensitivity to CRF in PTSD, rather than a decrease in the number of pituitary CRF receptors per se. This explanation is suggested by Smith et al (1989). Alternatively, however, in the absence of hypercortisolemia, a blunted ACTH response to CRF in PTSD could occur as a result of a hyperresponsivity of the pituitary gland to cortisol resulting directly from an increased number of glucocorticoid receptors on the pituitary gland (Yehuda et al 1990b).

The Distinctness of HPA Alterations in PTSD and Major Depressive Disorder

Table 3 summarizes the findings to date in major depressive disorder and PTSD on four measures of the HPA axis functioning. In the aggregate, studies of major depressive disorder suggest a decreased negative feedback sensitivity in one or more locations of the HPA axis. The components of this decreased feedback system are an overproduction of cortisol, a reduced number of glucocorticoid receptors, and, possibly, a neuronal defect

causing CRF hypersecretion. Whereas many questions remain concerning the etiology of HPA alterations in major depression and primary versus secondary defects, there is no major controversy concerning the direction of HPA alterations in this disorder.

In PTSD, the findings to date seem to suggest an enhanced sensitivity of the HPA feedback mechanism, resulting in a decreased basal cortisol level. The evidence supporting this are a reduced urinary cortisol excretion, an increased number of lymphocyte glucocorticoid receptors, and an apparently enhanced cortisol suppression to dexamethasone. An enhanced sensitivity of the HPA axis would potentially account for the blunted ACTH response to CRF: however, this possibility could be explored by measuring glucocorticoid receptors in conjunction with CRF challenges.

The elucidation of differences in HPA activity between PTSD and major depressive disorder may lead to information useful for diagnostic classification and treatment of these disorders. Furthermore, the HPA responses to acute, novel behavioral or pharmacological stress in subjects with PTSD must be clearly evaluated. Because there is no evidence for adrenal exhaustion as a mechanism for the baseline underactivity of the HPA axis in PTSD, it may be that individuals with PTSD show normal or heightened HPA responses to stress. An exaggerated response to novel stress would be consistent with preclinical studies of chronic stress as reviewed above. Further studies that allow for the evaluation of this interaction are needed to address this question.

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